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Carbon nanotubes as drug delivery nanocapsules

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Abstract

Nanotubes have been proposed as targeted drug delivery nanocapsules which may realize the "magic bullet" concept and promise many advantages over current procedures. The question arises as to whether a nanotube drug carrier could be engineered so that it is energetically favourable for the drug molecule to be encapsulated, and then once inside the cell, energetically favourable to be ejected. In other words, we need to understand and accurately predict the uptake and expulsion capacities of a particular carbon nanotube in association with the molecules of a particular drug. In this paper, for a carbon nanotube carrier, the concepts of an acceptance condition and the suction energy are used to determine the suction behaviour of cisplatin, a platinum-based anticancer drug. It is shown theoretically using elementary mechanics and applied mathematical modelling techniques that for cisplatin to be accepted, the carbon nanotube must have a radius of at least 4.785 Å, and that the maximum suction energy occurs when the carbon nanotube radius is 5.27 Å.

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Keywords: Drug delivery; Acceptance condition; Suction energy; Carbon nanotubes

1. Introduction

Nanocapsules have been proposed as a drug carrier that may be used to realize the "magic bullet" concept proposed by Paul Ehlrich [1] at the beginning of the 20th century, which refers to a drug capable of targeting a particular site and releasing its contents when desired. The nanocapsules are transported to the target site, such as a tumour, by their functionalized surface, and once at the designated site their contents are released in response to a trigger such as changed environmental conditions in the proximity of the target area. This targeted nature of drug delivery involves a much smaller dosage of the drug and will reduce currently observed adverse side effects. Current clinical procedures involve combining the drug with a solvent, which can cause additional adverse side effects. Nanocapsules offer advantages by enabling the drug to be encapsulated in a protective environment.

Presently nanoparticles are used as nanocapsules in areas such as drug delivery and cosmetics [2]. Current delivery methods include attaching both the drug and targeting antibodies to the outer surface, or diffusion of the drug through pores in the nanoparticle surface. Nanotubes have been suggested as a promising alternative, offering advantages such as distinct inner and outer surfaces which are readily accessible by removal of the end caps, and an increased volume [3] providing a higher payload capacity. Proposed filling techniques include immersing the nanotube in a solution containing the drug, attaching the drug to the inner tube wall surface [4], or by insertion in particle form [5]. Both nanoparticles [6,7] and nanotubes [8] have been shown to be readily taken up by cells, and it has been suggested that nanotubes may even enter the cell nuclei [9]. The question arises as to whether a nanotube drug carrier could be engineered so that it is energetically favourable for the drug molecule to be encapsulated, and then once inside the cell, it may be engineered so that it becomes energetically favourable to be ejected from the nanotube as a result of a trigger such as changed environmental conditions. In

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other words, we need to understand and predict the suction (or uptake) and expulsion capacities of a particular carbon nanotube in association with the molecules of a particular drug.

In this paper we examine the former issue only, and we present a synopsis of recent work [10] in which the suction behaviour of cisplatin, a platinum-based anticancer drug, and a carbon nanotube is examined. In the following section the procedure used to determine the interaction energy E [12] and the concepts of an acceptance condition and suction energy [11] are briefly defined. We then outline the suction behaviour of cisplatin and a carbon nanotube.

2. Uptake of cisplatin into a carbon nanotubes

The concepts of an acceptance condition and suction energy were first proposed by Cox et al. [11] in relation to predicting whether a C_{60} fullerene would be accepted into the interior of a carbon nanotube by van der Waals forces alone. In this section the concepts of an acceptance condition and suction energy [11] are briefly outlined and used to determine whether a particular drug will be accepted into the interior of a carbon nanotube, and to subsequently predict the radius of the nanotube that provides the maximum suction or uptake of the drug molecule. In particular, we examine the suction characteristics of the platinum-based, anticancer drug cisplatin. Cisplatin is one of the most frequently used anticancer drugs [13], used to treat tumours such as those of the ovary, testis, head and lung. These targeted nanocapsules may assist in reducing adverse side effects, such as kidney and nerve damage.

Initially we briefly define the interaction energy and interaction force, which are subsequently used to determine an acceptance condition and the suction energy. The interaction energy E is typically evaluated using either a discrete atom–atom formulation or by a continuous approach, where the atoms are assumed to be uniformly distributed over the surface of the molecule. Girifalco et al. [14] state that from "a physical point of view the discrete atom–atom model is not necessarily preferable to the continuum model", and that the continuum model may even be closer to reality. Here, a hybrid discrete–continuum formulation [12] is used which incorporates elements of both approaches, given by

$$E = \eta \sum_i \int \upsilon(\rho_i)\mathrm{d}S,$$

where η is the surface density of carbon atoms on the carbon nanotube, which is assumed to be that of graphene [11], 0.382 atoms/Å^2, ρ_i is the distance between a typical surface element dS on the nanotube and atom i in the drug molecule, $\upsilon(\rho_i)$ is the potential function, and we sum over all atoms in the drug molecule. A solely continuous approach requires regularly shaped molecules, and as such the hybrid method considered here enables drug molecules, which are normally irregularly shaped, to be represented discretely. The validity of this hybrid method is analyzed in Hilder and Hill [12] by comparison to both the continuum and discrete atom–atom approaches; there it was shown to give reasonable agreement with both approaches. In particular, when comparing the interaction of C_{60}, C_{70} and C_{80} with a carbon nanotube acceptance conditions are within 1% [11,12,15].

There are two major functional forms used to represent the potential function, $\upsilon(\rho_i)$: the inverse power model and the Morse function model [16,17]. In this investigation, the widely used Lennard-Jones inverse power model is adopted and is given by $\upsilon(\rho) = 4\varepsilon[-(\sigma/\rho)^6 + (\sigma/\rho)^{12}]$, where ε is the value of the energy at the equilibrium distance $\rho_0 = 1.12\sigma$, and σ is the atomic distance when the potential energy is zero. The Lennard-Jones potential is only applicable to non-polar interactions and as such this model represents a first approximation, since the drug molecule may also generate electrostatic interactions with the carbon nanotube. When the force constants between two distinct atoms are unavailable, as is the case in this investigation, they may be approximated by use of the empirical combining rules [18], namely $\varepsilon_{12} = (\varepsilon_1\varepsilon_2)^{1/2}$ and $\sigma_{12} = (\sigma_1 + \sigma_2)/2$, where the subscripts 1 and 2 refer to the respective individual atoms for the carbon nanotube [14] and the atoms corresponding to cisplatin [19,20]. In a solvent medium the interaction is much reduced and may be determined by reducing the interaction by a factor of the dielectric constant [10,18].

Using the algebraic package MAPLE we plot the interaction energy and interaction force. The van der Waals interaction force $F(Z)$ is given by the negative gradient of the interaction energy E, thus $F(Z) = -\mathrm{d}E/\mathrm{d}Z$, where Z is the distance between the centre of mass of the drug molecule and the end of the carbon nanotube, and we assume a semi-infinite nanotube. The drug's centre of mass is assumed to be located on the carbon nanotube axis and only one orientation of cisplatin is presented [10]. Fig. 1 illustrates the interaction energy of cisplatin for nanotubes

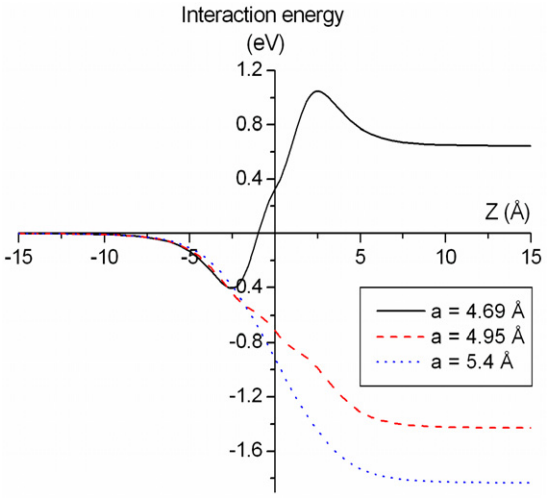

Fig. 1. Energy for cisplatin entering a nanotube of varying radii.

of radii 4.69, 4.95, and 5.4 Å. Similarly, the interaction force is shown in Fig. 2 for a nanotube of radius 4.69 Å.

With reference to Fig. 2, for a molecule assumed initially at rest and located on the tube axis, to be accepted into the interior of a carbon nanotube the following inequality [11] must hold true

$$\int_{-\infty}^{-Z_0} F(Z)\mathrm{d}Z > 0, \tag{1}$$

where Z_0 is the positive root of the interaction force $F(Z)$, as shown in Fig. 2, and this is the formal mathematical condition for a molecule to enter the carbon nanotube. The left-hand side of Eq. (1) is termed the acceptance energy, and may be plotted against the nanotube radius to determine the minimum radius of nanotube that will accept the particular drug molecule. Consequently, a carbon nanotube must have a radius of at least 4.785 Å for a cisplatin molecule to be accepted into its interior. Acceptance is further illustrated by Fig. 1 in which a drug molecule will be accepted if the energy inside the tube (positive Z) is less than the energy outside the tube (negative Z). Following this, and with reference to Fig. 1, a nanotube with radius 4.69 Å will not be accepted, but the other two radii will be accepted into the carbon nanotube interior.

The suction energy S is defined as the total energy generated by van der Waals interactions acquired as a consequence of being sucked into the carbon nanotube [11], or more formally

$$S = \int_{-\infty}^{\infty} F(Z)\mathrm{d}Z.$$

Fig. 3 illustrates the resulting suction energy of cisplatin with a carbon nanotube of varying radius a. In the range $4.74 < a < 4.785$ Å the suction energy is not necessarily sufficient to overcome the energy barrier at the tube end, but it is energetically favourable for cisplatin to be inside the carbon nanotube if it can overcome this barrier. It is only possible for the carbon nanotube to accept cisplatin in this range if additional energy is applied to cisplatin by some external force. Maximum suction is shown to occur when the nanotube has a radius of 5.27 Å. For full details of the derivation and the approach used here we refer the reader to Hilder and Hill [10].

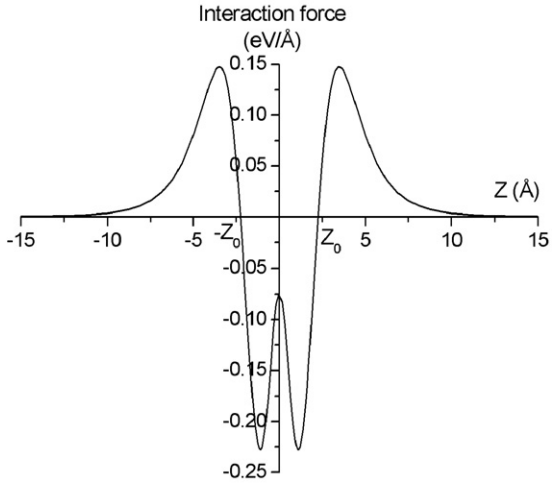

Fig. 2. Force for cisplatin and a nanotube of radius 4.76 Å.

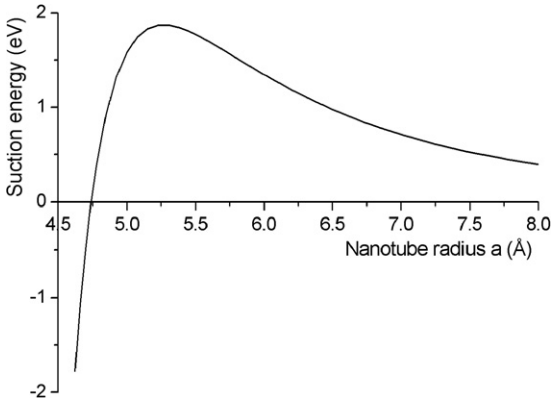

Fig. 3. Suction energy for cisplatin entering a carbon nanotube.

3. Conclusions

In this paper we use an acceptance condition and the suction energy to determine the suction behaviour of a particular drug molecule entering a nanotube. In order to determine the acceptance and suction characteristics, an interatomic interaction energy must be evaluated, and we use the hybrid discrete–continuum formulation [12], where the acceptance condition is shown to be within 1% of typically used models. This energy is subsequently used to examine the suction behaviour of the anticancer drug cisplatin [10]. The nanotube radius must be greater than 4.785 Å to accept cisplatin into its interior, and the maximum suction energy occurs when the nanotube radius is 5.27 Å. This paper presents a synopsis of recent work by the authors [10] which presents for the first time calculations of this nature in an area where there has been very little experimental and molecular dynamics studies. Results presented here may be extended to other drug molecules and used to provide guidelines for medical scientists when engineering nanocapsule drug delivery vehicles.

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